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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Songtao Shi

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KLARQUIST SPARKMAN, LLP
121 S.W. SALMON STREET
SUITE #1600
PORTLAND, OR 97204-2988

EXAMINER

FALK, ANNE MARIE

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/553,633	Applicant(s) SHI ET AL.	
	Examiner Anne-Marie Falk, Ph.D.	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 December 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 59-65, 67, 68, 71-78, 80-86, 88-90 and 92-108 is/are pending in the application.
- 4a) Of the above claim(s) 67, 68, 71-78, 80-86, 88-90, 92-102 and 108 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 59-65 and 103-107 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 19 October 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>10/19/05 & 10/12/09</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The amendment and response filed December 9, 2009 has been entered. Applicants' election, without traverse, of Group I, Claims 59-65, is acknowledged. Claims 59-65, 67, 68, 71, 75, 76, 78, 80, 81, 82, 85, 86, 88, 89, 90, 92, 94, and 95 have been amended. Claims 66, 69, 70, 79, 87, and 91 have been canceled and Claims 103-108 have been newly added.

Accordingly, Claims 59-65, 67, 68, 71-78, 80-86, 88-90, and 92-108 are pending in the instant application.

Claims 67, 68, 71-78, 80-86, 88-90, 92-102, and 108 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 9, 2009.

Accordingly, Claims 59-65 and 103-107 are examined herein.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 59-65 and 103-107 are rejected under 35 U.S.C. 102(a) as being anticipated by Gronthos et al. (August 2002, J. of Dental Research 81(8): 531-535).

Claim 59 is directed to an isolated human postnatal deciduous dental pulp multipotent stem cell, wherein the stem cell differentiates into a neural cell, an adipocyte, or an odontoblast, and wherein the stem cell expresses CD146.

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Gronthos et al. (2002) disclose isolated postnatal human dental pulp stem cells (DPSCs) as instantly claimed. Although the cells of Gronthos et al. were isolated from third molars collected from adults aged 19-29 years, the cells appear to be identical to dental pulp stem cells isolated from deciduous teeth and meet all the claim limitations. Thus, although the claims recite the source of the claimed stem cell, the source is treated as a product-by-process limitation and is given patentable weight only insofar as it implies structural limitations. Once a reference teaching a product appearing to be substantially identical is made the basis of a rejection, and evidence or reasoning tending to show inherency is presented, the burden shifts to the applicant to show an unobvious difference. The DPSCs disclosed by Gronthos et al. are multipotent and are capable of differentiating into adipocytes and neural cells (see abstract). After culturing DPSCs in an adipogenic-inductive cocktail for 5 weeks, Oil red O-positive lipid clusters were identified in the cultures (page 534, column 1, paragraph 2 and Figure 3A). Up-regulation of two adipocyte-specific transcripts, PPARgamma2 and lipoprotein lipase, was also found (page 534, column 1, paragraph 2 and Figure 3B). The reference further discloses that DPSCs express nestin and glial fibrillary acidic protein (GFAP) (page 534, column 1, paragraph 2 and Figures 3C-3G). Thus, the reference explicitly discloses all the limitations of Claims 59, 61, 62, 63, and 64.

The reference further discloses that dental pulp stem cells implanted subcutaneously into immunocompromised mice gave rise to odontoblasts which produced a dentin-pulp-like complex containing organized collagen fibers. The regenerated dentin was immunoreactive for human dentin sialoprotein (DSP) antibody (page 534, column 1, paragraph 1 and page 532, column 1, paragraph 2). Dentin sialoprotein and dentin phosphoprotein are encoded by a single gene known as DSPP (dentin sialophosphoprotein). Thus, the reference demonstrates that the disclosed dental pulp stem cells can differentiate into an odontoblast, as set forth in Claim 59, and that the cells express DSPP, as recited in Claim 62.

Thus, the claimed invention is disclosed in the prior art.

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Claims 59-65 and 103-107 are rejected under 35 U.S.C. 102(b) as being anticipated by Gronthos et al. (2000, PNAS 97(25): 13625-13630).

Claim 59 is directed to an isolated human postnatal deciduous dental pulp multipotent stem cell, wherein the stem cell differentiates into a neural cell, an adipocyte, or an odontoblast, and wherein the stem cell expresses CD146.

Gronthos et al. (2000) disclose isolated postnatal human dental pulp stem cells (DPSCs) as instantly claimed. Although the cells of Gronthos et al. were isolated from molars collected from adults aged 19-29 years, the cells appear to be identical to dental pulp stem cells isolated from deciduous teeth and meet all the claim limitations. Thus, although the claims recite the source of the claimed stem cell, the source is treated as a product-by-process limitation and is given patentable weight only insofar as it implies structural limitations. Once a reference teaching a product appearing to be substantially identical is made the basis of a rejection, and evidence or reasoning tending to show inherency is presented, the burden shifts to the applicant to show an unobvious difference. The DPSCs are multipotent and express CD146 (as set forth in Claim 59), alkaline phosphatase (ALP, as set forth in Claims 61 and 62), and osteocalcin (as set forth in Claim 63) (page 13627, column 1, paragraph 1 and Table 1). Table 1 shows that clonal cells give rise to progeny that include various subpopulations of cells with distinct protein expression profiles, thereby demonstrating that the cells are multipotent. For example, the clonal cell line DPSC-1 gives rise to progeny that strongly express MUC-18/CD146, as well as cells that do not express MUC-18/CD146 at all.

Gronthos et al. also disclose that dental pulp stem cells implanted subcutaneously into immunocompromised mice generate a dentin-like structure comprised of a highly ordered collagenous matrix perpendicular to an odontoblast-like layer (page 13627, column 2, paragraph 2), thereby demonstrating the properties recited in Claims 106 and 107. The reference further discloses that the odontoblast-like cells were found to be of donor origin (page 13628, column 1). Thus, the reference

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demonstrates that the disclosed dental pulp stem cells can differentiate into an odontoblast, as set forth in Claim 59.

Thus, the claimed invention is disclosed in the prior art.

Claims 59-65 and 103-107 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 02/07679 (Shi et al., January 2002).

Claim 59 is directed to an isolated human postnatal deciduous dental pulp multipotent stem cell, wherein the stem cell differentiates into a neural cell, an adipocyte, or an odontoblast, and wherein the stem cell expresses CD146.

Shi et al. (January 2002) disclose isolated postnatal human dental pulp stem cells (DPSCs) as instantly claimed. Although the cells of Shi et al. were isolated from molars collected from adults aged 19-29 years (page 9), the cells appear to be identical to dental pulp stem cells isolated from deciduous teeth and meet all the claim limitations. Thus, although the claims recite the source of the claimed stem cell, the source is treated as a product-by-process limitation and is given patentable weight only insofar as it implies structural limitations. Once a reference teaching a product appearing to be substantially identical is made the basis of a rejection, and evidence or reasoning tending to show inherency is presented, the burden shifts to the applicant to show an unobvious difference. The DPSCs are multipotent and express CD146 (as set forth in Claim 59), alkaline phosphatase (ALP, as set forth in Claims 61 and 62), and osteocalcin (as set forth in Claim 63) (page 13, paragraph 2 and Table 1). Table 1 shows that clonal cells give rise to progeny that include various subpopulations of cells with distinct protein expression profiles, thereby demonstrating that the cells are multipotent. For example, the clonal cell line DPSC-1 gives rise to progeny that strongly express MUC-18/CD146, as well as cells that do not express MUC-18/CD146 at all.

Shi et al. also disclose that dental pulp stem cells implanted subcutaneously into immunocompromised mice generate a dentin-like structure comprised of a highly ordered collagenous

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matrix perpendicular to an odontoblast-like layer (page 14, paragraph 2), thereby demonstrating the properties recited in Claims 106 and 107. The reference further discloses that the odontoblast-like cells were found to be of donor origin (page 14, lines 18-20). Thus, the reference demonstrates that the disclosed dental pulp stem cells can differentiate into an odontoblast, as set forth in Claim 59.

Thus, the claimed invention is disclosed in the prior art.

Claims 59-65 and 103-107 are rejected under 35 U.S.C. 102(b) as being anticipated by Shi et al. (2001, 29(6): 532-539), as evidenced by Gronthos et al. (2000, PNAS 97(25): 13625-13630) and Gronthos et al. (August 2002, J. of Dental Research 81(8): 531-535).

Claim 59 is directed to an isolated human postnatal deciduous dental pulp multipotent stem cell, wherein the stem cell differentiates into a neural cell, an adipocyte, or an odontoblast, and wherein the stem cell expresses CD146.

Shi et al. (2001) disclose isolated human postnatal dental pulp multipotent stem cells as instantly claimed. The study undertaken compared the gene expression profiles of human dental pulp stem cells (DPSCs) and bone marrow stromal stem cells (BMSSCs). Although the cells of Shi et al. were isolated from third molars collected from adults aged 19-31 years (page 533, column 1, paragraph 2), the cells appear to be identical to dental pulp stem cells isolated from deciduous teeth and meet all the claim limitations. Thus, although the claims recite the source of the claimed stem cell, the source is treated as a product-by-process limitation and is given patentable weight only insofar as it implies structural limitations. Once a reference teaching a product appearing to be substantially identical is made the basis of a rejection, and evidence or reasoning tending to show inherency is presented, the burden shifts to the applicant to show an unobvious difference. The cells of Shi et al. were isolated according to the method previously described by Gronthos et al. (2000, PNAS 97(25): 13625-13630) (page 533, column 1, paragraph 2), and therefore are the same cells previously described by Gronthos et al. (2000). Shi et al. further disclose that the human DPSCs express transcription factor Cbfa1 (page 536, column 2, paragraph

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2), as set forth in Claims 62 and 63, and FGF-2 (page 536, columns 1-2), as set forth in Claim 61 (FGF-2 is also known as basic fibroblast growth factor). Shi et al. further disclose that the human DPSCs express alkaline phosphatase (page 536, column 1), as set forth in Claims 61 and 62.

Inherent properties of the cells disclosed by Shi et al. are disclosed by Gronthos et al. (2000, PNAS 97(25): 13625-13630). Gronthos et al. (2000) disclose that DPSCs are multipotent and express CD146 (as set forth in Claim 59), alkaline phosphatase (ALP, as set forth in Claims 61 and 62), and osteocalcin (as set forth in Claim 63) (page 13627, column 1, paragraph 1 and Table 1). Table 1 shows that clonal cells give rise to progeny that include various subpopulations of cells with distinct protein expression profiles, thereby demonstrating that the cells are multipotent. For example, the clonal cell line DPSC-1 gives rise to progeny that strongly express MUC-18/CD146, as well as cells that do not express MUC-18/CD146 at all. Gronthos et al. also disclose that dental pulp stem cells implanted subcutaneously into immunocompromised mice generate a dentin-like structure comprised of a highly ordered collagenous matrix perpendicular to an odontoblast-like layer (page 13627, column 2, paragraph 2). The reference further discloses that the odontoblast-like cells were found to be of donor origin (page 13628, column 1). Thus, the reference demonstrates that the disclosed dental pulp stem cells can differentiate into an odontoblast, as set forth in Claim 59.

Inherent properties of the cells disclosed by Shi et al. are also disclosed by Gronthos et al. (August 2002, J. of Dental Research 81(8): 531-535). Gronthos et al. (2002) disclose that isolated postnatal human dental pulp stem cells (DPSCs) are multipotent and are capable of differentiating into adipocytes and neural cells (see abstract). After culturing DPSCs in an adipogenic-inductive cocktail for 5 weeks, Oil red O-positive lipid clusters were identified in the cultures (page 534, column 1, paragraph 2 and Figure 3A). Up-regulation of two adipocyte-specific transcripts, PPARgamma2 and lipoprotein lipase, was also found (page 534, column 1, paragraph 2 and Figure 3B). The reference further discloses that DPSCs express nestin and glial fibrillary acidic protein (GFAP) (page 534, column 1, paragraph 2 and Figures 3C-3G). Thus, the reference explicitly discloses all the limitations of Claims 59 and 64. The

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reference further discloses that dental pulp stem cells implanted subcutaneously into immunocompromised mice gave rise to odontoblasts which produced a dentin-pulp-like complex containing organized collagen fibers. The regenerated dentin was immunoreactive for human dentin sialoprotein (DSP) antibody (page 534, column 1, paragraph 1 and page 532, column 1, paragraph 2). Dentin sialoprotein and dentin phosphoprotein are encoded by a single gene known as DSPP (dentin sialophosphoprotein). Thus, the reference explicitly demonstrates that human dental pulp stem cells can differentiate into an odontoblast, as set forth in Claim 59, and that the cells express DSPP, as recited in Claim 62.

Thus, the claimed invention is disclosed in the prior art.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

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Claim 65 is rejected under 35 USC § 103(a) as being obvious over Gronthos et al. (2000, PNAS 97(25): 13625-13630) and Nakashima et al. (June 2002, Gene Therapy 9(12): 814-818).

Claim 65 is directed to the stem cell of Claim 59, wherein the cell is transfected with a nucleic acid.

Gronthos et al. (2000) disclose isolated postnatal human dental pulp stem cells (DPSCs) as instantly claimed. Table 1 shows that clonal cells give rise to progeny that include various subpopulations of cells with distinct protein expression profiles, thereby demonstrating that the cells are multipotent. For example, the clonal cell line DPSC-1 gives rise to progeny that strongly express MUC-18/CD146, as well as cells that do not express MUC-18/CD146 at all. Although the cells of Gronthos et al. were isolated from molars collected from adults aged 19-29 years, the cells appear to be identical to dental pulp stem cells isolated from deciduous teeth and meet all the claim limitations. Thus, although the claims recite the source of the claimed stem cell, the source is treated as a product-by-process limitation and is given patentable weight only insofar as it implies structural limitations. Once a reference teaching a product appearing to be substantially identical is made the basis of a rejection, and evidence or reasoning tending to show inherency is presented, the burden shifts to the applicant to show an unobvious difference. The isolated human postnatal dental pulp multipotent stem cell of Gronthos et al. is substantially identical to the isolated human postnatal dental pulp multipotent stem cell of Claim 1. The reference further discloses the usefulness of *ex vivo* expanded DPSCs in conjunction with carriers of appropriate shape and composition in making viable dental implants (page 13630, column 2, last sentence).

Nakashima et al. (2002) disclose that dental pulp stem cells transfected with a cDNA construct encoding growth/differentiation factor 11 (Gdf11) differentiate into dentin-forming odontoblasts. The plasmid encoding Gdf11 also included a gene encoding green fluorescent protein (GFP), which was used as a marker to identify transfected cells (page 816, paragraph bridging columns). The authors note that

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the results of their study “provide the scientific basis and rationale for gene therapy for endodontic treatments in oral medicine and dentistry” (abstract).

Since one of skill in the art would have been motivated to use transfected dental pulp stem cells expressing Gdf11 to develop therapeutic protocols for endodontic treatments, as explicitly noted by Nakashima et al., the skilled artisan would have immediately recognized that human therapeutic protocols would require the use of human dental pulp stem cells. Thus, the skilled artisan would have transfected the cells of Gronthos et al. with a vector encoding Gdf11 to generate human dental pulp stem cells that can be expanded in culture and differentiated into odontoblasts for transplantation-based therapeutic protocols. Alternatively, one of skill in the art would also have been motivated to transfect human dental pulp stem cells with a vector encoding GFP, as disclosed by Nakashima et al., for transplant studies similar to those carried out by Gronthos et al. This would allow the skilled artisan to readily distinguish donor cells from host cells by detecting expression of GFP *in situ*. One of skill in the art would readily recognize that transfection of donor cells with a vector encoding GFP (or any reporter) is a well-known technique in transplant studies for distinguishing donor cells from host cells. Thus, multiple motivations would have led one of skill in the art to transfect human dental pulp stem cells with a nucleic acid.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Conclusion

No claims are allowable.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (571) 272-0728. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on (571) 272-4517. The central official fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Anne-Marie Falk, Ph.D.

/Anne-Marie Falk/
Primary Examiner, Art Unit 1632